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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/560,563	02/15/2007	T. Keith Blackwell	10276-093US1	6644

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EXAMINER	
BERTOGLIO, VALARIE E	
ART UNIT	PAPER NUMBER
1632	

NOTIFICATION DATE	DELIVERY MODE
01/02/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PATDOCTC@fr.com

Office Action Summary	Application No.	Applicant(s)	
	10/560,563	BLACKWELL ET AL.	
	Examiner	Art Unit	
	Valarie Bertoglio	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11/07/2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18,27-34,36,38* is/are pending in the application.

4a) Of the above claim(s) *5-8, 14-18,27-34,36 and 38* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,9-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12/12/2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *07/22/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Sequence Compliance Form*.

DETAILED ACTION

Applicant's election without traverse of Group I, claims 1-4 and 9-13 in the reply filed on 11/07/2008 is acknowledged.

Claims 5-8, 14-18,27-34,36 and 38 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 11/07/2008.

Specification

The disclosure is objected to because of the following informalities: The specification refers to various colors in the drawings. However the drawings are not in color. See page 16, Figure 5, for example.

Appropriate correction is required.

Sequence Compliance

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. **The application contains sequences that are not identified with a sequence identifier, i.e. SEQ ID NO:1. For example, see Figures 1,3,7-36,39.** Applicants must file a "Sequence Listing" accompanied by directions to enter the listing into the specification as an amendment. Applicant also must provide statements regarding sameness and new matter with regards to the CRF and the "Sequence Listing."

Applicant is given ONE MONTH, or THIRTY DAYS, whichever is longer, from the mailing date of this letter within which to comply with the sequence rules, 37 CFR 1.821 - 1.825. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 CFR 1.821(g). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a). In no case may an applicant extend the period for reply beyond the SIX MONTH statutory period. Direct the reply to the undersigned. Applicant is requested to return a copy of the attached Notice to Comply with the reply. Failure to fully comply with the sequence rules in response to the instant office action will be considered non-responsive.

Claim Rejections - 35 USC § 112-1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4 and 9-13 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for

1) a method for determining whether a test compound is a candidate SKN-1-mediated oxidative stress response-activating compound, comprising: (a) providing a first nematode capable of expressing a SKN-1 polypeptide and containing at least one transgene comprising an oxidative stress resistance gene promoter operably linked to a reporter gene *wherein the promoter comprises a SKN-1 binding site effective at driving constitutive and stress-induced expression*; (b) contacting the first nematode with the test compound; and (c) determining whether expression of said at least one transgene is increased in said first nematode *compared to a control nematode not contacted with said test compound*, wherein an increase in expression of the transgene in the nematode contacted with the test compound compared to the control

nematode indicates that the test compound is a candidate SKN-1-mediated oxidative stress response-activating compound (claim 1), and

2) a method for determining whether a test compound is a candidate SKN-1-mediated oxidative stress response-inhibiting compound, comprising: (a) providing a first nematode capable of expressing a SKN-1 polypeptide and containing at least one transgene comprising an oxidative stress resistance gene promoter operably linked to a reporter gene *wherein the promoter comprises a SKN-1 binding site effective at driving constitutive and stress-induced expression*; (b) contacting the first nematode with the test compound; (c) subjecting the nematode to conditions that are known activate the SKN-1 mediated oxidative stress response in the absence of the test compound, and (d) determining whether expression of said at least one transgene is decreased in said first treated nematode *compared to a control nematode not contacted with said test compound*, wherein a decrease in expression of the transgene in the nematode contacted with the test compound compared to the control nematode indicates that the test compound is a candidate SKN-1-mediated oxidative stress response-inhibiting compound (claim 3), and

3) said methods further comprising determining if the test compound binds either GSK-3 or SKN-1 or is a potentially inhibitor of GSK-3 or SKN-1 activity (claims 2 and 4),

does not reasonably provide enablement for the claimed method wherein the oxidative stress promoter does not comprise SKN-1 responsive elements or wherein there is no control for comparison or for definitively determining that the test compound is an inhibitor of GSK-3 or SKN-1 activity. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key

word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

The invention is related to methods of screening for modulators of oxidative stress genes. Specifically, claim 1 is drawn to a method of screening for agents that increase expression of oxidative stress genes modulated by the SKN-1 transcription factor. Claim 3 is drawn to a method of screening for agents that decrease expression of oxidative stress genes modulated by the SKN-1 transcription factor.

Relevant to claim 1, the specification provides teachings at pages 53-55, Table 2 and Figure 2. The specification teaches use of a SKN-1 expressing nematode that is transgenic for transgene comprising the gcs-1 promoter operably linked to GFP. The gcs-1 promoter comprises 3 SKN-1 responsive elements and removal of various elements was shown to differentially affect promoter activity (pages 54-56). Pharyngeal expression was found to be SKN-1 independent and relies on distal elements affected by other transcription factors (page 54). Thus, removal of SKN-1 elements did not alter pharyngeal GFP expression highlighting the fact that oxidative stress-induced genes can be activated through other mechanisms. Within the proximal region of the gcs-1 promoter that comprises three SKN-1 elements, only the third element was found to be necessary for intestinal, oxidative stress responsive GFP expression. The specification teaches treating the transgenic worms with various oxidative stress inducing

agents such as heat and paraquat and comparing GFP expression to untreated controls (see Table 2 and description of Figure 2).

The claims are overly broad in that they encompass use of nematodes that lack essential SKN-1 responsive elements that drive oxidative stress induced expression. The specification has taught that oxidative stress–responsive genes can be regulated by non-stress related factors through binding elements other than SKN-1 binding elements. The specification has also taught use of promoters wherein the necessary and effective SKN-1 responsive elements are removed. The invention requires comparison of reporter gene expression between treated and untreated nematodes wherein oxidative stress induces SKN-1 activity in the nucleus. Without the appropriate SKN-1 binding elements in the transgene, oxidative stress would not alter expression of the associated reporter, regardless of the presence of SKN-1.

The claims are also broad in that they fail to recite to what the treated nematode is compared. The specification appears to compare treated nematodes to untreated controls to determine an increase in reporter gene expression. However, this is not recited in the claims. An increase cannot be determined without a baseline for comparison. Claims 9 and 10 add a method step wherein a second, untreated nematode is used, however, this step occurs after steps of claims 1 and 3, respectively, which are not enabled. Claim 3 requires correlation of a decrease or no change in transgene expression to an oxidative stress response inhibiting compound. A lack of change is presumed to indicate that an expected increase does not occur in response to stress-inducing conditions. However, if a comparison is made to an untreated control that has been subject to stress-inducing conditions, the comparison would be noticed as a decrease. A lack of change in expression would be observed only if the comparison is to the expression level of the same first nematode before subject to stress and to the test agent. The claim is broader than this scenario. The claims have been deemed enabled only for comparison to an untreated control, however, this untreated control can be the first nematode prior to treatment. In claim 3, the claim should

be amended to remove reference to "unchanged" or should narrow the conditions under which "unchanged" is indicative of an inhibiting compound.

Claims 2 and 4 are not enabled for determining whether the candidate compounds are active inhibitors of GSK-3 or SKN-1, respectively. The specification gives prophetic and generic support to further screening identified compounds from claims 1 and 3 to determine if they bind to GSK-3 or SKN-1 (see page 4, lines 20-24 and page 10, lines 6-11, for example). While one would presume that an activator of the oxidative stress pathway that binds GSK-3 would be an inhibitor of GSK-3 and an inhibitor of the oxidative stress response that binds SKN-1 would be an inhibitor of SKN-1, this conclusion cannot be definitively made. The specification only supports determination of binding activity and fails to provide any means to determine that the compounds are active inhibitors. To determine inhibition of activity, an activity assay would be necessary and this is not supported by the specification.

Claim Rejections - 35 USC § 112-2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-4 and 9-13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 3 recite the limitation "the transgene" in lines 8 and 11, respectively. There is insufficient antecedent basis for this limitation in the claim. The claim requires the nematode comprise "at least one transgene". Thus, it is not clear which transgene "the transgene" is referring to. It is presumed that the claim is referring to multiple copies of the same transgene. However, the claim reads more broad

than this and thus, "the transgene" may be interpreted as referring to a particular transgene, the identity of which is not clearly set forth by the claim.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Valarie Bertoglio whose telephone number is (571) 272-0725. The examiner can normally be reached on Mon-Thurs 5:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Valarie Bertoglio/
Primary Examiner
Art Unit 1632